Halogenated Sesquiterpene Phenols and Ethers from the Red Alga *Laurencia glandulifera* Kützing[1]

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Several brominated sesquiterpene phenols and the related ethers were isolated from the red alga *Laurencia glandulifera* Kützing. The structures of these compounds were determined on the basis of spectroscopic evidence and chemical correlation.

In the course of our continuing studies of the constituents of the red algae genus *Laurencia* (Rhodomelaceae), we have reported a variety of metabolites which have been isolated from *L. glandulifera* Kützing, *i.e.*, laurencin,[2] several halogenated chamigrenes,[3,4] spirolaurenone,[5] two bromocuparenes,[6] and laurene.[7] In a previous communication[8] we reported the isolation and structural elucidation of three brominated aromatic sesquiterpene ethers as minor components from this alga. The isolation of these ethers prompted us to investigate the remaining portion of the neutral oil of this alga, and three brominated phenols were isolated. We wish to report herein the isolation and structures of these minor brominated sesquiterpene phenols, (**1a**), (**2a**), and (**3a**), and the related ethers, (**8**), (**9**), and (**10**).

Freshly collected and half-dried algae were extracted with MeOH in the usual manner. The neutral MeOH extracts, which, on silica gel TLC, reveal a chromatogram similar to that of the previous extracts, were fractionated by column chromatography on neutral alumina.

Sesquiterpene Phenols: Diethyl ether fractions, which consisted of a mixture of alcohols, were rechromatographed on a silica-gel column. The earlier benzene eluates afforded a mixture of phenols which, following acetylation, was further submitted to preparative TLC on silica gel to yield three acetylated products, (**1b**), (**2b**), and (**3b**).

The major compound (**2b**) was identified as the acetate of laurenisol (**2a**), isolated from *L. nipponica* Yamada,[9] by a direct comparison of their physical properties.

One of the minor compounds, **1b**, $C_{17}H_{20}O_2Br_2$ (*m/e* 418, 416, and 414; M^+), had the following spectral characteristics: ν_{max} 1760 cm^{-1}; δ 0.73 (3H, d, J= 7 Hz), 1.14, 2.25, 2.36 (each 3H, s), 2.85 (1H, q, J=7), 6.01 (1H, br s), 6.85, and 7.27 (each 1H, s). The IR and NMR spectra of **1b** are very similar to those of laurenisol acetate (**2b**). In the NMR spectra of **1b** and **2b**, however, distinct differences were observed in the lower-field region; *e.g.*, in the spectrum of **2b**, absorptions due to three aromatic protons appeared at 6.75 (1H, br s), 6.85 (1H, br d, J=8), and 7.01 (1H, d, J=8) instead of two aromatic protons in the spectrum of **1b**. Hence, **1b** must be a bromo analog of laurenisol acetate (**2b**). Saponification of **1b** with 5% methanolic KOH gave the original phenol (**1a**). The structure of **1a** was confirmed by the following reaction: laurenisol (**2a**) was treated with bromine in acetic acid under the same conditions as the bromination of debromolaurinterol (**6a**)[10] to yield a brominated product, which was found to be identical with **1a** in all respects.

Another minor compound (**3b**), $C_{17}H_{21}O_2Br$ (*m/e* 338 and 336; M^+), $[\alpha]_D^{25}$ +45°, indicates in its IR and NMR spectra the presence of a secondary methyl group [0.66 (3H, d, J=7) and 2.70 (1H, q, J=7)], which was shifted to the higher magnetic field as same as **1b** and **2b**, a tertiary methyl group [1.12 (3H, s)], an aromatic methyl group [2.27 (3H, s)], a 2,4,5-trisubstituted phenyl acetate grouping [1763 cm^{-1}; 2.36 (3H, s), 6.84 and 7.25 (each 1H, s)], and a terminal methylene group [1655 and 885 cm^{-1}; 4.80 and 4.90 (each 1H, br s)]. These spectral data reveal that **3b** has a structure similar to that of **1b** except for a terminal methylene group instead of a bromomethylene group in **1b** and would, therefore, be represented by formula **3b**, an isomer of laurinterol acetate (**5b**) and isolaurinterol acetate (**7b**).[10] The spectral properties were identical to those reported[11] for the acetate of allollaurinterol (**3a**), isolated from *L. filiformis* as a major metabolite[11,12] and *L. subopposita* as a minor one.[13] Debromoallolaurinterol (**4a**) was also isolated from *L. subopposita*.[13]

Although the stereochemistry of a double bond between C-3 and C-6 in **2a** has remained unsettled, the assignment of the *Z*-configuration to this double bond can now be made with the aid of chemical shifts of the proton at C-2 in the NMR spectra of **1a**, **2a**, **3a**, and **4a**. In these spectra, the signals of C_2–H in **1a** (δ 3.11 q) and **2a** (δ 3.15 q) appear in a lower-field region than those in **3a** (δ 2.95 q) and **4a** (δ 2.95 q). These low-field chemical shifts in **1a** and **2a** are due to the deshielding being caused by C_6–Br, which is situated close to C_2–H.

Sesquiterpene Ethers: The hexane fraction was repeatedly chromatographed on a silica-gel column and subsequently on a PLC to yield three bromo ethers, (**8**), (**9**), and (**10**), along with laurene, isolaurene, bromocuparenes, and halo-chamigrenes.[4]

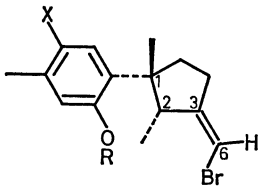
One of the three bromo ethers, **8**, $C_{15}H_{19}OBr$ (*m/e* 296 and 294; M^+), was identified as the ether isomerized from laurenisol (**2a**)[9] by comparisons of the spectral data.

The second bromo ether, **9**, mp 86—87 °C, $[\alpha]_D^{23}$ +22°, $C_{15}H_{18}OBr_2$ (*m/e* 376, 374, and 372; M^+), shows in its NMR spectrum the presence of three methyl groups at 0.74 (3H, d, J=7), 1.38 (3H, s), and 2.29 (3H, s), a $BrCH_2$-group at 3.41 and 3.55 (each 1H, AB-q, J=10), and two aromatic protons at 6.55 and 7.08 (each 1H, s). The IR and NMR spectra of **9** are very similar to those of **8**, suggesting that **9** must be a bromo analog of **8**. The structure

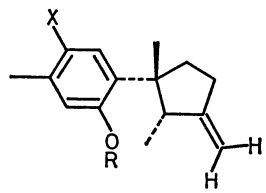
of **9** was confirmed by the following reactions. Treatment of **8** with bromine in acetic acid yielded a dibromo compound, which was identical with **9** in all respects. Although, on treatment with *p*-toluenesulfonic acid in acetic acid at room temp (2 h), **1a** was recovered, treatment of **1a** with TsOH in acetic acid under reflux gave **9** in a low yield.

The third bromo ether, **10**, mp 125—126 °C, $[\alpha]_D^{21}$ +79°, $C_{15}H_{18}OBr_2$ (*m/e* 376, 374, and 372; M^+), shows in its IR and NMR spectra the presence of three methyl groups [0.68 (3H, d, J=7), 1.35 (3H, s), and 2.22 (3H, s)], a Br_2CH-group [5.65 (1H, s)], and a 2,5-substituted aryl ether moiety [1622, 1577, 1505, 1245, and 815 cm^{-1}; 6.50 (1H, br s), 6.50 (1H, br d, J=8), and 6.82 (1H, d, J=8)].

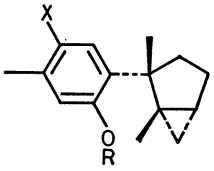
The NMR spectrum of **10** displays signals comparable to those of **8** except for the absorptions due to a two-proton quartet at δ 3.40 and 3.52 (attributed to the $BrCH_2$-group in **8**) instead of a one-proton singlet at δ 5.65 (attributed to the Br_2CH-group in **10**). Thus, formula **10** can completely interpret all spectral properties. The related compounds, filiformin (**11**) and filiforminol (**12**), were also isolated from *L. filiformis*.[11,12]



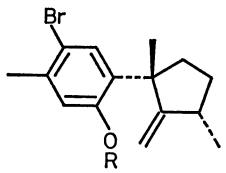
1a: X = Br, R = H
1b: X = Br, R = Ac
2a: X = H , R = H
2b: X = H , R = Ac



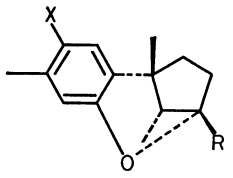
3a: X = Br, R = H
3b: X = Br, R = Ac
4a: X = H , R = H



5a: X = Br, R = H
5b: X = Br, R = Ac
6a: X = H , R = H



7a: R = H
7b: R = Ac



8: X = H , R = CH_2Br
9: X = Br, R = CH_2Br
10: X = H , R = $CHBr_2$
11: X = Br, R = CH_3
12: X = Br, R = CH_2OH

Experimental

All the mps were uncorrected. The IR spectra were measured on a Nihon-Bunko IR-S spectrometer in a $CHCl_3$ soln. The NMR spectra were recorded on a JEOL JNM-PS-100 spectrometer, TMS being used as the internal reference in a CCl_4 soln. The optical rotations were measured in a $CHCl_3$ soln. Alumina (Merck, activity II—III) and silica gel (Mallinckrodt, 100 mesh) were used for the column chromatography. Silica gel (Merck, Kieselgel GF_{254} (Type 60)) was used for the preparative TLC (PLC).

Isolation. *L. glandulifera* was collected at Oshoro Bay Hokkaido, early in August, 1978. The half-dried algae (600 g) were extracted with methanol. After the separation of the acidic and basic components by shaking with 1M aqueous KOH and 1M aqueous HCl respectively, a neutral oil (7.3 g) was obtained; this oil was subsequently chromatographed on a neutral alumina column. Elution with hexane gave an oily substance, which consisted of a mixture of hydrocarbons, aromatic ethers, and fatty acid methyl esters. Elution with ether gave a mixture of alcohols, which was then rechromatographed on a silica-gel column. The earlier benzene eluates gave a mixture of phenolic compounds, which was acetylated with acetic anhydride in pyridine at room temp in the usual manner and subsequently chromatographed on a PLC plate to give **1b** (0.5% of neutral oil), **2b** (0.2%), and **3b** (0.07%). These acetates were converted to the original phenols, (**1a**), (**2a**), and (**3a**), by treatment with 5% KOH in methanol. The above oily substance eluted with hexane was rechromatographed on a silica-gel column. The later hexane eluates were further repeatedly chromatographed on a PLC plate to yield **8** (0.07%), **9** (0.05%), and **10** (0.05%). These phenols and ethers were also obtained from the previous extracts but in different ratios.

1a: Colorless oil; $[\alpha]_D^{22}$ +74° (*c* 0.58); IR, ν_{max} 3680, 3360, 1640, 1610, 1500, 1397, 1380, 1255, 1150, 1070, and 885 cm^{-1}; NMR, δ 0.73 (3H, d, J=7 Hz), 1.19 (3H, s), 2.28 (3H, s), 3.11 (1H, q, J=7 Hz), 4.60 (s: OH), 5.98 (1H, br s), 6.47 (1H, s), and 7.13 (1H, s); MS, *m/e* (rel. intensity) 376, 374, 372 (7, M^+), 361, 359, 357 (2), 295, 293 (21), 253, 251 (7), 214 (53), 199 (21), 149 (47), 115 (16), 91 (18), 77 (18), 71 (58), 57 (55), and 43 (100). Acetate **1b**: colorless oil; $[\alpha]_D^{20}$ +76° (*c* 0.95); IR, ν_{max} 1760, 1642, 1375, 1190, 1147, 1070, and 908 cm^{-1}; MS, *m/e* 418, 416, 414 (4, M^+), 403, 401, 399 (1), 376, 374, 372 (10), 337, 335 (46), 295, 293 (53), 294, 292 (51), 279, 277 (23), 265, 263 (14), 214 (100), 201 (25), 199 (28), 159 (10), 145 (11), 115 (11), 91 (13), 77 (10), and 43 (65).

2a and **3a**: **2a** and **3a** were identified as laurenisol and allolaurinterol respectively by comparisons of the spectral data of the corresponding acetates, **2b** and **3b**. Attempts to crystallize **3b** [white solid, $[\alpha]_D^{25}$ +45° (*c* 0.35)] failed; allolaurinterol acetate,[11] mp 86.6—89.1 °C (from methanol), $[\alpha]_D$ +48.2° (*c* 1.03 in $CHCl_3$).

8: The IR and NMR spectra were superimposable on those of an authentic sample (**8**).[9]

9: Mp 86—87 °C (from methanol); $[\alpha]_D^{23}$ +22° (*c* 1.16); IR, ν_{max} 1612, 1557, 1395, 1380, 1357, 1240, 1152, 1085, 1020, 935, and 880 cm^{-1}; MS, *m/e* 376, 374, 372 (8, M^+), 295, 293 (17), 239, 237 (14), 214 (29), 201 (13), 199 (15), 107 (100), 95 (43), and 91 (27).

10: Mp 125—126 °C (from methanol); $[\alpha]_D^{21}$ +79° (*c* 0.38); IR, ν_{max} 1622, 1577, 1505, 1390, 1355, 1308, 1245, 1175, 1150, 1083, 1017, 965, 872, and 815 cm^{-1}; MS, *m/e* 376, 374, 372 (46, M^+), 295, 293 (35), 214 (40), 213 (100), 201 (50), 159 (51), 135 (30), 133 (20), 121 (30), 105 (15), and 91 (20).

Conversion of ***2a*** *to* ***1a***. One molar equivalent of bromine (8 mg) in acetic acid (2 ml) was added to a soln of **2a** (15 mg) in acetic acid (1 ml). The mixture was allowed to stand at room temp for 15 min and then extracted with ether. The ether soln was successively washed with water, 5% aqueous $NaHCO_3$, and saturated brine, and dried over Na_2SO_4. A crude substance obtained after the removal of the solvent was chromatographed on a PLC plate to give **1a** (18 mg); The IR and NMR spectra were superimposable on those of natural **1a**.

*Conversion of **8** to **9**.* One molar equivalent of bromine (21 mg) in acetic acid (2 ml) was added to a soln of **8** (40 mg) in acetic acid (1 ml). The mixture was allowed to stand at room temp for 15 min and then worked up as has been described above. Crude crystalline products were chromatographed on a PLC plate to give **9** (38 mg); crystals; mp 85 °C; The IR and NMR spectra were superimposable on those of natural **9**.

*Conversion of **1a** to **9**.* A soln of **1a** (16 mg) and *p*-toluenesulfonic acid (15 mg) in acetic acid (1 ml) was refluxed for 30 min. The mixture was then poured into water and extracted with ether. The ether soln was successively washed with water, 5% aqueous $NaHCO_3$, and saturated brine, and dried over Na_2SO_4. Crude products were chromatographed on a PLC plate to give **9** (6 mg).

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